ONLINE FIRST

Urinary Iodine Excretion After Contrast Computed Tomography Scan

Implications for Radioactive Iodine Use

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Importance: Patients who undergo radiographic studies with contrast receive an enormous bolus of iodine. This can delay subsequent use of radioactive iodine (RAI) therapy because the iodine can compete for uptake. There is a paucity of literature on the minimum interval between contrast administration and RAI therapy.

Objective: To better characterize how long it takes for the iodine load from an intravenous contrast bolus to clear from the body.

Design, Setting, and Participants: A prospective cohort of 21 adults undergoing intravenous contrast CT studies at a tertiary academic medical center; exclusion criteria included history of thyroid disease or thyroidectomy, history of renal insufficiency, pregnancy, and other contrast administration within 1 year.

Intervention: Morning urine samples were taken before the scan for analysis and then every 2 weeks thereafter for 12 weeks.

Results: The median baseline iodine level was 135 μg/L (range, 29-1680 μg/L), and median peak level was 552 μg/L (range, 62-6172 μg/L). Median time for urinary iodine level to normalize was 43 days, with 75% of subjects returning to baseline within 60 days, and 90% of subjects within 75 days. Baseline iodine level was a significant predictor of postcontrast iodine levels. Age, sex, weight, and estimated glomerular filtration rate were not significant.

Conclusions and Relevance: These results may be used for guidance on the timing of RAI use following contrast exposure. The practice at our institution is to wait 2 months and then check a 24-hour urinary iodine level. This alleviates concerns about contrast use in patients with thyroid carcinoma interfering with adjuvant radioiodine therapy.

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RADIOGRAPHIC STUDIES SUCH as computed tomography (CT) scans are commonly performed with intravenous contrast, which contains an enormous amount of iodine. A typical chest CT study uses about 100 mL of intravenous contrast material, which translates to about 30 g of iodine. The content of free iodide, according to manufacturer regulations, is far less than the total amount of organically bound iodine, with an upper limit of 50 000 μg/L, but this still means a single contrast-enhanced CT scan gives an adult over 30 times the minimum daily allowance of dietary iodine (5000 μg vs 150 μg). (To convert iodine to nanomoles per liter, multiply by 7.880.) Deiodination of the contrast medium molecules in the body can further introduce 0.01% to 0.15% more free inorganic iodine.[1]

In healthy patients, iodine diffuses into extracellular spaces and then follows 2 competitive pathways: uptake by the thyroid gland or excretion in urine. Administration of large doses of iodine and contrast medium causes a transient decrease in thyroid hormone synthesis through the Wolff-Chaikoff effect. This causes a compensatory increase in TSH level, but this effect generally does not increase iodine levels beyond normal limits except in some geriatric patients or patients with other risk factors like hyperthyroidism, who may develop iodine-induced thyrotoxicosis.[1] Renal iodine clearance rate is not influenced by iodine intake; it is not adaptive and not saturable.[2]

The inorganic iodine introduced in the contrast bolus can also compete with radioactive iodine (RAI) for uptake and reduce the efficacy of diagnostic or therapeutic radioiodine use in patients with, for example, differentiated thyroid carcinoma. Patients may also present for evaluation of thyroid nodules identified inci-

dentally on a contrasted CT scan performed for another indication. In addition, the benefit of contrasted CT scans sometimes outweighs the problem of RAI interference, such as in the identification of cervical and mediastinal disease that cannot be imaged by sonography.

The minimum time between contrast exposure and RAI administration is not well established. The American Thyroid Association Guidelines for the Management of Differentiated Thyroid Carcinoma recommend that "iodinated contrast should be avoided if radioactive iodine (RAI) therapy is planned within the subsequent few months."[3(p1195)] Other literature suggests that a single iodinated contrast exposure is likely to compromise radioiodine uptake for 3 to 12 months, so it has been recommended that contrast not be given to patients who may need radioiodine therapy or radioiodine whole-body scans over the next year.[4]

The goal of the present study was to assess the kinetics of urinary iodine excretion after contrast CT scan to provide better guidance on how long radioiodine therapy should be delayed.

METHODS

The study population consisted of 24 adults undergoing intravenous contrast CT studies. Study subjects were recruited such that the cohort had equal numbers of men and women and equal numbers of individuals aged between 21 and 39 years and between 40 and 70 years. Reflecting the demographic characteristics of our area, nearly all patients were white. Exclusion criteria were history of thyroid disease or thyroidectomy, history of renal insufficiency, contrast administration within the last 6 months, and pregnancy. Three subjects did not return their study specimens, and so a final total of 21 participants were included in the analysis. All gave written informed consent. The study was approved by the institutional review board at the University of Iowa Hospitals and Clinics.

Study participants were asked to submit a baseline urine sample taken from the first void on the morning of their CT scan. Following their scan, they then collected an additional morning urine sample every 2 weeks. The specimens were mailed out for iodine level measurement (Mayo test No. 8639, cost $92 per specimen). The time for each patient's iodine level to return to the baseline, pre-CT level was recorded. Because iodine levels can also be affected by other factors such as diet, subjects were also considered "back to baseline" when the levels reached an inflection point from a decreasing trend to a higher value. Demographic information about the participants, as well as their weight and serum creatinine level, were recorded from medical chart review and used for calculation of estimated glomerular filtration rate. The creatinine levels were not available for 2 men and 2 women group aged 21 to 39 years, and 1 man in the group aged 40 to years, but all reported normal renal function.

Time-to-baseline data were analyzed by computing a Kaplan-Meier estimate to estimate median and 75th and 90th percentiles. The effects of covariates on time to baseline were assessed using log-rank tests. Statistical analysis was performed using SAS software, version 9.2 (SAS Institute Inc).

RESULTS

Baseline iodine levels ranged from 29 to 1680 μg/L, with outliers at the high end creating a positive skew (median, 135 μg/L; mean [SD], 233 [235] μg/L). The subjects received 75 mL to 147 mL of iopamidol contrast (Isovue-370; Bracco Imaging Group) as determined by Department of Radiology protocols for the particular examination (eg, 75 mL for a chest CT scan and 147 mL for an abdomen and pelvis CT scan). Peak iodine levels ranged from 62 to 6172 μg/L (median, 552 μg/L; mean [SD], 1052 [1567] μg/L). The **Table** lists the ranges, medians, and means of urinary iodine levels for the groups categorized by age and sex and by the length of time to return to baseline for these groups.

Table. Urinary Iodine Levels and Time for Levels to Return to Baseline by Patient Age and Sex

Patient Age Group, y	Urinary Iodine Level, μg/L[a]		Time to Return to Baseline, Mean (SD) (Range), d
	Baseline, Median (Range)	Peak, Median (Range)	
21-39			
Men (n = 4)	149 (29-527)	331 (62-629)	41 (21) (28-71)
Women (n = 5)	186 (38-1680)	385 (258-6172)	50 (11) (32-59)
40-70			
Men (n = 6)	171 (46-336)	758 (122-1493)	53 (17) (42-84)
Women (n = 6)	117 (42-233)	906 (324-5097)	50 (20) (32-76)

[a] There was a wide range of urinary iodine levels.

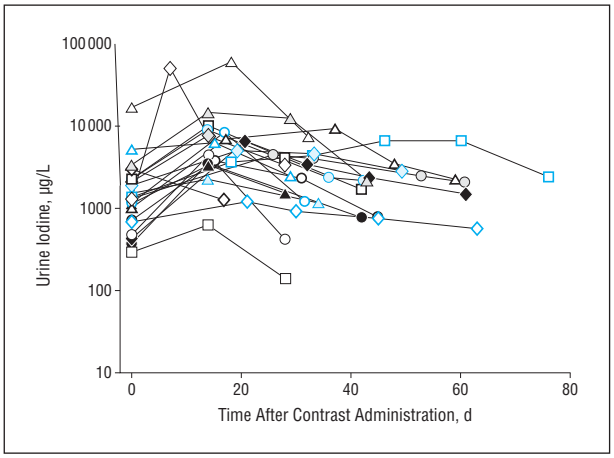

Figure 1. Serial changes in urinary iodine levels of individual subjects over time after receiving contrast. Each line represents 1 patient. Most peak values were observed in the first postscan measurement, but in 3 individuals (14%), the peak occurred at a later date. The implications of this are unclear.

Figure 1 shows the serial changes in urinary iodine levels of individual subjects over time after receiving contrast. Most peak values were observed in the first postscan urine specimen, but in 3 individuals (14%), the peak occurred after the first 2 weeks.

Kaplan-Meier analysis (**Figure 2**) estimated a median time of 43 days to return to baseline. The 75th percentile for time to baseline was 59 days, and the 90th percentile was 74 days. Patients older than 40 years did not experience a delayed return of iodine level to baseline compared with younger patients (median, 42.5 days for older patients vs 45.0 days for patients younger than 40 years) (P = .25). There were no differences in time to baseline between men and women (median, 42.5 days for men vs 45.0 days for women) (P = .99).

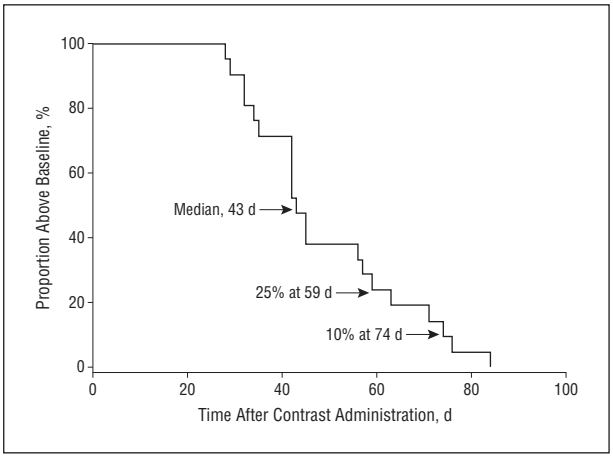

Figure 2. Kaplan-Meier analysis demonstrated a median time of 43 days to return to baseline. The 75th percentile for time to baseline was 59 days, and the 90th percentile was 74 days.

DISCUSSION

The administration of iodine-containing contrast media is known to suppress thyroidal RAI uptake.[5,6] It has been speculated that release of free inorganic iodides is responsible for this,[7] but the exact mechanism for inhibition of RAI uptake has not been clearly demonstrated. The precise level of iodide necessary to induce inhibition has also not been determined, although Childs et al[8] demonstrated that intravenous exposure to 100 μg of iodide could suppress thyroid uptake in patients with hyperthyroidism. These studies from the 1950s measured the return to baseline of radioactivity levels after administration of contrast and RAI to human subjects, but such study methods have not been repeated using the nonionic contrast agents used nowadays. The use of nonionic contrast media has been credited with decreasing the frequency of overall adverse events from about 30% to 5%.[9] However, Laurie et al[10] demonstrated that current agents, including Isovue, still contain free iodine levels capable of suppression. Furthermore, Nygaard at al[11] found a 53% reduction in median RAI uptake at 1 week after injection of iohexol, an early nonionic contrast agent not used today.

Existing clinical recommendations for RAI use after exposure to iodinated contrast primarily reference a study by Costa et al.[12] That study examined the iodine levels in nonthyroid tissues (eg, fat, brain, muscle) taken from biopsy or autopsy specimens of 24 subjects after administration of a variety of drugs with iodine or contrast media for other reasons and compared these against the levels in subjects who were not exposed. Almost all were tested within 1 month; 2 were tested at 1 year. Of the subjects tested at 1 year, one demonstrated nearly normal levels, while the other showed elevated levels. A single subject tested at 29 months showed elevated iodine levels. These studies have been interpreted differently with respect to the timing of RAI use.

Radioactive iodine is used after thyroidectomy to ablate the residual thyroid remnants, as adjuvant therapy for thyroid cancers, and to treat metastases. The indications for RAI use are currently evolving as more is understood about recurrence risk in differentiated thyroid cancer. There is increased understanding about the effects of different doses of RAI on ablation success, and some advocate for a dosimetric approach. The long-term, dose-related complications risks of RAI are also being recognized, such as radiation sialadenitis and second primary malignant neoplasms.[13] To maximize efficacy of the RAI and reduce risk to other sites in the body, it is therefore important to avoid interference in thyroidal RAI uptake by other sources of iodine. For this reason, patients must be asked about contrast exposure. In addition, surgical disinfectants such as povidone-iodine are replaced with non–iodine-containing solutions for thyroidectomies,[14] and patients are restricted to low-iodine diets prior to RAI treatment.[15] Urinary levels of iodine are normally in the range of 1000 μg/L to 4000 μg/L, and a urinary iodine level of 1000 μg/L or lower is targeted before RAI administration.[4]

Because urinary iodine level is widely used as the clinical criteria for determining preparedness for RAI therapy, it is what we chose to measure in our study. However, urinary iodine level is a surrogate measurement used in lieu of body iodine because it can be measured noninvasively. In addition, there is heterogeneity in the method of urinary iodine level measurement–the American Thyroid Association Guidelines[3] recommend a spot urinary iodine determination, while others use a 24-hour urinary iodine. We chose to test the first morning void for this study because it was more convenient for study participants to collect and return in the mail than the full 24-hour amount. Age- and sex-adjusted iodine-creatinine ratio is a better approximation of the 24-hour excretion than iodine concentration[16] but was not necessary for this study since results were only compared within subjects for trending back to baseline levels. A fasting morning specimen reduces the effects of diurnal variation.

At our institution, a 24-hour urinary iodine study is routinely conducted prior to administration of RAI. In the setting of recent contrast administration, this is done after a 2-month interval, based on the findings of our study. However, other practitioners may elect to risk delaying therapy and wait a longer period (eg, 75 days) so that 90% of patients would be expected to have adequate iodine levels, which carries the benefit of eliminating the expense and effort of repeated testing. We believe it is useful to verify the urinary iodine level for any patient about to undergo RAI therapy regardless of whether she received contrast, since the efficacy of RAI treatment and risk of adverse effects like radiation sialadenitis are dependent on the dose uptake. Also, individuals can have a wide range of urinary iodine levels at baseline, as seen in our results.

A longer interval between contrast administration and RAI may be chosen for patients older than 40 years. That age was chosen for our group analysis because after age 40 years, the glomerular filtration rate is expected to decrease progressively with age. Interestingly, we found that the estimated glomerular filtration rate, as calculated from the patient's age, sex, race, and creatinine level using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, was not significant. However, since our study excluded individuals with renal disease, no conclusions could be drawn about iodine excretion with impaired renal function. In addition, nearly all partici-

pants were white, so the effect of race on contrast iodine excretion could not be assessed. Diet was not controlled in this study, and so dietary iodine intake, rather than a return to baseline, was likely the reason urinary iodine levels reached an inflection point in some patients.

In conclusion, these results may be used for guidance on the timing of RAI use following contrast exposure. The practice at our institution is to wait 2 months, and then take a 24-hour urinary iodine measurement. The finding that 75% of patients' levels returned to baseline within 59 days, and 90% within 75 days, provides guidance to clinicians about the timing of RAI therapy. Although urinary iodine level was chosen as the measure for this study because it is widely used to determine preparedness for RAI, the actual relationship of the urinary iodine level to RAI uptake, successful thyroid ablation, thyroid cancer recurrence rates, and ultimately to survival outcomes remains an active area of research.

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